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Original Communication

Unclassified sudden infant death associated with pulmonary intra-alveolar hemosiderosis and hemorrhage

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Abstract

The significance of severe pulmonary intra-alveolar hemosiderosis in sudden infant death is controversial in forensic pathology. We report a previously healthy 9-month-old female infant who died suddenly and unexpectedly after being placed and then found prone in her crib. Her gestation and delivery were uncomplicated, and she had no history of anemia, hemoptysis, chest trauma, or chronic lung disease. Autopsy revealed diffuse severe pulmonary congestion and severe multifocal intra-alvedar hemorrhage. Metabolic and toxicological screening, microbiologic cultures, and vitreous chemistry were noncontributory. A diagnosis of SIDS had been made by the medical examiner. Subsequent semiquantitative assessment of the severity of pulmonary intra-alveolar hemosiderosis prompted consideration of other disorders, including a heretofore undescribed lethal infantile variant of idiopathic pulmonary hemosiderosis, but none could be confirmed. Therefore, we assigned a study diagnosis of unclassified sudden infant death. We recommend that a diagnosis of SIDS not be made in cases with unexplained large numbers of intra-alveolar PS. We also recommend that quantitative assessment of lung sections stained for iron be undertaken in cases with numerous intra-alveolar macrophages in order to accumulate data that might allow diagnostic correlations with the circumstances of death and autopsy findings.

Keywords: Sudden infant death; Idiopathic pulmonary hemosiderosis; Suffocation; SIDS

1. Introduction

The significance of pulmonary intra-alveolar siderophages (PS) in cases of sudden infant death is unclear, and has been a matter of some controversy. From a forensic perspective, they have been proposed as a tissue marker that could possibly aid in distinguishing SIDS from "soft" suffocation.[1–7] Indeed, when PS are present in large numbers, some investigators suggest that SIDS is an inappropriate diagnosis.[1,5,8] In our previous study, we found that the number of PS varies widely in cases of sudden infant death caused by SIDS and accidental or inflicted suffocation, and cannot be used as an independent variable to ascertain past attempts at suffocation.[9] However, other less sinister causes must be considered as well. We present a case of sudden unexpected infant death that was found to have large numbers of PS associated with moderately severe hemorrhage, and discuss the possible etiology.

2. Case report

A 9-month-old Caucasian female was somewhat fussy with a poor appetite when she was placed alone and prone to sleep in a crib by her day care provider. About 2 h later

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she was found prone and unresponsive. Cardiopulmonary resuscitation (CPR) was attempted for 62 min but was unsuccessful.

She was delivered vaginally at 40 weeks gestation following the uncomplicated pregnancy of her mother who had regular prenatal care. Her birth weight was 3060 g (<25th percentile). She was breastfed and received formula supplements. Her immunizations were current at the time of her death. One month prior to her death, she had been successfully treated with antibiotics for otitis media; several days prior to her death signs of "ear pulling" recurred, but in the absence of a fever, a physician was not consulted. There was no history of hemoptysis, apnea, pneumonia, allergies, or chest injuries. Sudden infant or childhood death had not occurred among siblings. The family history was negative for allergies, smoking, drug use, and contact with police or social services. The household was free of fumes, peeling paint, and mold growth.

Autopsy by the San Diego County Office of the Medical Examiner (ME) revealed a normally-developed female infant measuring 70 cms (25th percentile) in length and weighing 7110 g (<5th percentile). The postmortem radiographs revealed no evidence of trauma or underlying disease in the skeleton including the ribs and spine. The bladder was empty. Thymic, epicardial, and pleural petechiae were present. The middle ears were not examined.

The right and left lungs weighed 76 and 68 g, compared with expected weights of 59 and 53 g,[35] respectively; the cut surfaces were medium to dark maroon and oozed bloody fluid. Parenchymal consolidation, thromboembolism, infarction, fibrosis, and vascular thickening were not identified. Postmortem toxicology, microbiologic cultures of blood and CSF, and metabolic screening were negative. Vitreous chemistry was noncontributory. Middle ear and lung cultures were not performed.

The ME identified diffuse severe pulmonary congestion and moderately severe intra-alveolar hemorrhage, but not other significant pathologic findings. Our microscopic examination revealed grade 3 pulmonary intra-alveolar hemorrhage (PH) when assessed semiquantitatively in hematoxylin and eosin (H&E) stained sections of formalin-fixed lung using the following grading system: grade 0 = none; 1 = mild; 2 = moderate, focal; 3 = moderate, multifocal; and 4 = diffuse, severe.[10]

We also identified large numbers of pulmonary intra-alveolar siderophages (PS) in iron-stained tissue from both lungs (Fig. 1). PS were counted in 20 randomly selected but contiguous 400× high-power fields (hpf) in each of the four available lung sections stained by the Prussian blue method, as previously described.[9] PS count (defined here as the average number of PS per 20 hpf per lung section) was 1732 in this case.[9] Eosinophils and mast cells were neither increased nor degranulated when evaluated in appropriately controlled Giemsa stained lung sections. Appropriately controlled Masson trichrome and Verhoff-van Gieson elastic stained lung sections did not reveal evidence of pulmonary fibrosis or hypertensive arteriopathy.

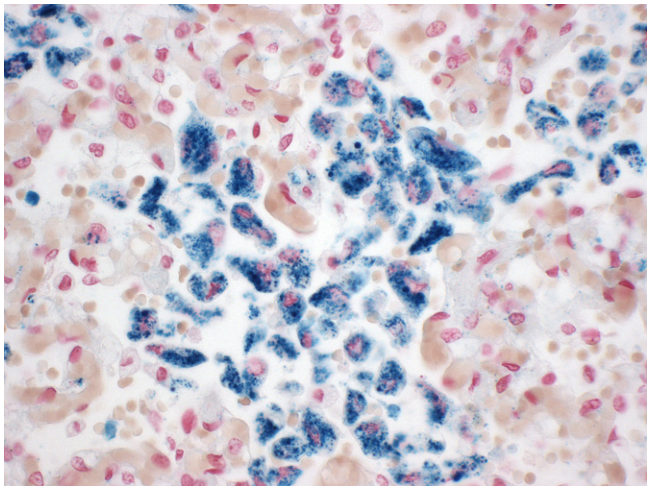

Fig. 1. Lung section in a 9-month-old female, with severe pulmonary hemosiderosis. The average number of pulmonary intra-alveolar siderophages per 20 randomly selected but contiguous fields per section was 1732. Prussian blue stain, 400×.

IgG, IgA, IgM, C3, C1q, properdin, fibrinogen, and albumin were not present in microscopic lung sections that were deparaffinized and reprocessed for immunofloures-cence microscopy (IF). Immunoglobulin controls consisting of plasma cells in tonsil tissue stained appropriately.

3. Discussion

We have presented a 9-month-old, term born female infant who died suddenly and was found at postmortem examination to have moderately severe pulmonary hemorrhage. As part of our previous study,[9] we had identified a particularly large number of diffusely distributed PS in this case, prompting us to re-evaluate the cause of death. Since accidental asphyxia and other causes of death were excluded, we considered sudden infant death syndrome (SIDS), inflicted suffocation, and idiopathic pulmonary hemosiderosis (IPH). In fact, her death was initially ascribed to SIDS by the ME (Case 9, Table 5[9]). The most current general definition for SIDS is "the sudden and unexpected death of an infant under one year of age, with onset of the lethal episode apparently occurring during sleep, that remains unexplained after a thorough investigation including performance of a complete autopsy, and review of the circumstances of death and the clinical history".[11] Our case was within the classic SIDS age range and apparently died during sleep; further, she had been placed and found prone in an otherwise safe sleep environment, and at autopsy, had an empty bladder and intrathoracic petechiae. Ancillary autopsy analyses did not explain the death.

In our initial study, we found a wide range of PS in cases of SIDS as well as accidental and inflicted suffocation, indicating that numerous PS can not be used independently to exclude SIDS.[9] However, the PS count in the present case (1732) was exceptionally high; the mean

among our SIDS cases was 97 ± 264. Further, 80% (73 of 91) of our SIDS cases had <100 PS count and 96% (87 of 91) had <600 PS count.[9] Given the particularly large number of PS in this case compared to remainder of the SIDS cases from our earlier study, as well as the SIDS cases reported by Schluckebier et al. in which 100% had <5 PS per lung lobe,[7] SIDS does not appear to be a tenable diagnosis.

Inflicted suffocation after prior failed attempts was also considered since PS have been proposed as a possible diagnostic tissue marker.[1] In an analysis of 43 cases with a variety of causes of death, Schluckebier et al. concluded that PS may be a marker for repeated asphyxia or hypoxia, but not SIDS.[7] Conversely, Forbes and Acland concluded from their literature review that previous episodes of imposed suffocation are not proven by the presence of PS.[12] In our study, the mean PS count in cases of accidental and inflicted suffocation was 47 ± 64; the PS counts in the two inflicted suffocation cases were 117 and 10.4.[9] These numbers are very low in comparison to the present case with a PS count of 1732. Our case had no clinical history of ALTEs, and oronasal blood (ONB) was not present at the time of discovery. ONB has been documented after attempted suffocation;[13] conversely, it is rare in SIDS infants found supine, alone, and in a safe sleeping environment.[14] Old or acute injuries, including on the face or oronasal mucus membranes, and postmortem radiographic evidence suggestive of abuse were not found at autopsy. In addition, there was no record that the family had been referred to Child Protective Services prior to the infant's death.

Idiopathic pulmonary hemosiderosis (IPH) was also considered. It is a rare disorder with an estimated incidence per million children of 0.24 cases in Sweden[15] and 1.23 cases in Japan.[16] The youngest and oldest ages of onset of IPH reported to date are 4 weeks[17] and 47 years; but 80% of cases occur in children.[18] The etiology of IPH is currently unknown, but environmental pesticides and toxins,[19] mold infections[20] (later refuted[21]) and allergic reactions to cow's milk protein[22,23] (also later refuted[24]) have been considered. Familial clustering of IPH cases in Arizona and Greece suggests a hereditary component.[24,25] None of these factors were identified in our case.

The clinical presentation and course of IPH are variable and are dependent on the duration of disease prior to diagnosis or death. Iron deficiency anemia is common in children,[17,25,26] but less so in adults.[25] The clinical course is often characterized by chronic or recurrent cough, hemoptysis, and dyspnea evolving into pulmonary hemosiderosis and fibrosis.[18] Fever, cough and malaise occur in most cases, but dyspnea was reported in less than 50% of the cases.[25] Functional lung defects were identified in three of four pediatric cases undergoing lung biopsy.[27] Sudden death is caused by acute pulmonary hemorrhage (PH) while delayed death usually follows chronic pulmonary insufficiency.

In IPH, recurrent lung hemorrhage leads to accumulation of PS as well as septal fibrosis, alveolar epithelial cell hyperplasia and degeneration, and increased mast cells.[28] IF is characteristically negative, as in our case. Electron microscopy reveals absence of electron deposits and intact alveolar capillary basal lamina.[24,29–31]

Despite the diagnostic importance, semiquantitative assessment of PS severity in IPH has only been attempted in one previous report. In this single study, the number of PS was based upon evaluation of 10 microscopic fields apparently examined at a magnification of 20×.[8] However, it is not clear if the counts were limited to intra-alveolar siderophages, or if interstitial siderophages were included.[8] The magnitude of PS counts may be important when correlated with the medical history, circumstances of death, and autopsy, but at the present time, data are far too scarce to propose that there may be a reliable value above which a diagnosis of IPH could be made with confidence.

In infants, the clinical symptoms of IPH may be subtle or even unrecognized. For example, an infant was treated unsuccessfully for iron deficiency anemia for several months before IPH was recognized as its cause (personal communication, Dr. T.G. Keens, December 2005). In another report, a diagnosis of IPH was established by chest radiography and BAL findings 50 days after onset of anemia in a 2-year 4-month-old female with microcytic hypochromic anemia unresponsive to iron therapy.[32] Gross hemoptysis is uncommon in infants and pallor may be difficult to recognize if the anemia is mild. Our case was fussy, perhaps suggesting she was becoming ill. Patients with IPH may be more likely to bleed during viral illnesses. Anemia was not identified clinically in our case, but the postmortem bone marrow specimen revealed erythroid hyperplasia.

It should be emphasized that the existent literature has not associated IPH with sudden death during infancy, even with onset during the first 12 months of life.[15,18,25,26,28,33] When an infant or child with a history fulfilling diagnostic clinical criteria dies and numerous PS are identified at autopsy, the diagnosis of IPH should not be difficult.[15,26,28] But a diagnosis of IPH should also be considered in cases of sudden infant death with large numbers of PS and significant pulmonary hemorrhage unexplained after an exhaustive search for other causes. Previous reports identifying the clinical onset of IPH during infancy do not specify if those who died did so suddenly before their first birthdays.[25,34]

In the final analysis, IPH deserves serious diagnostic consideration, especially since there are no known confounding factors suggestive of another diagnosis.

In conclusion, we favor categorizing this case as an example of unclassified sudden infant death (USID) recently defined for those cases not meeting "the criteria for Category l or II SIDS, but where alternative diagnoses of natural or unnatural conditions are equivocal."[11]

We recommend that: (1) A diagnosis of SIDS not be made in sudden infant death cases with unexplained large numbers of PS, (2) Postmortem lung sections be stained for iron in cases of sudden unexpected infant death with

large numbers of intra-alveolar macrophages, especially since the number of PS can be severely underestimated in H&E stained sections, and (3) Quantitative assessment of PS be undertaken to accumulate data that might allow future studies to more reliably correlate their presence with the circumstances of death and postmortem findings.

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